ASPREVA
PHARMACEUTICALS

27 June 2005

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Division of Dockets Management
HFA-305
Food and Drug Administration
3650 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2005-0106, CDER 2004127

Dear Sir/Madam,

I am forwarding to you a hard-copy of Aspreva Pharmaceuticals' response to the above docket, which was submitted in electronic form via email on 27 June, 2005. If there are any questions, please do not hesitate to contact me.

Yours sincerely,

Alison Sinclair

Alison Sinclair
Clinical Research Scientist
Aspreva
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2005D-0106 C2

ASPREVA
PHARMACEUTICALS

26 June 2005

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket Number 2005D-0106, CDER 2004127

Dear Sir/Madam,

Aspreva Pharmaceuticals is an emerging pharmaceutical company focused on identifying, developing and commercializing new indications for approved drugs and drug candidates for underserved patient populations. Aspreva's "indication partnering" strategy allows its partners to maintain core brand focus while extending the benefits of their medicines to a broader patient population. Since 2003, the Company has been in collaboration with Hoffmann La Roche, Inc. to develop CellCept (mycophenolate mofetil) for various autoimmune indications, including lupus nephritis.

The Company is appreciative that FDA has prepared a draft guideline, "Guidance for Industry, Systemic Lupus Erythematosus – Developing Drugs for Treatment, March 2005". Aspreva believes that the Guidance, in its final form, will provide helpful insight to companies involved in the development of new therapeutics for this underserved area of medicine. Aspreva is in a unique position to comment on this document since the Company has recently launched a large and complex Phase III clinical trial with CellCept to treat lupus nephritis patients. This study will address treatment in the acute induction of remission stage, as well as the more long term maintenance phase. The program which will enrol 358 patients at over 100 sites around the world, will take 4-5 years to complete.

The challenges and alternatives faced by companies involved in developing clinical programs in SLE have been extensively documented in the Concept Paper for Systemic Lupus Erythematosus and the proceedings of the Advisory Committee meeting held in 2003. The draft Guidance continues that effort, but to be truly useful to industry, however, Aspreva recommends that the Guidance be more specific in capturing the Agency's thinking about the design of lupus studies that are ultimately approvable. The Guidance should lay out a clear road-map to regulatory approval for those involved with this area of clinical research. Unfortunately, while great effort has been expended to produce the current draft Guidance, this guideline more effectively documents the challenges already identified elsewhere rather than clearly stating what is required for regulatory approval.

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Specifically, Aspreva believes that clear and direct guidance in the following areas would be useful:

- Concurrence of comparable approaches across all Divisions of FDA dealing with lupus and its manifestations
- Statistical considerations in study design (non-inferiority vs. superiority)
- Identification of suitable surrogate endpoints
- Acceptability of potential accelerated approval pathways for therapies in this underserved area (Subpart H and Subpart E)

In the attached document, detailed comments have been provided. In each case, the section of the text from the draft Guidance has been reproduced, followed by the comment from Aspreva.

Aspreva welcomes the opportunity to comment on this draft Guideline and remains available to discuss the Company comments at FDA's convenience.

Sincerely,

Lawrence D. Mandt
Vice President
Regulatory Affairs

Comments on Draft Guidance for Industry: Systemic Lupus Erythematosus – Developing Drugs for Treatment (Federal Register, 70 FR 15868)

Aspreva Pharmaceuticals Corp.

FINAL: June 27 2005

General comment

The Agency has presented a somewhat general summary of clinical trial methodology. However, clinical trial methodology in this indication has not been well-defined since relatively few pivotal clinical trials for registration have been submitted and critiqued as part of the regulatory approval process. Given the lack of standardization in methodology and the acknowledged complexity of systemic lupus erythematosus (SLE) and its manifestations, the Agency may want to consider providing more specific direction in this Guidance, particularly with respect to the definition of endpoints that are appropriate for the active and stable phases of disease. As part of the Critical Path Initiative, the Agency may wish to offer more specific advice on the analysis of multiple endpoints, design of noninferiority studies, the selection of safety endpoints for analysis, and adaptive/flexible designs that may increase the likelihood of success in clinical development programs in SLE.

As SLE is a multisystem disease, submissions involving lupus may be considered by different Divisions, depending upon the manifestation of the disease. This Guidance should indicate how submissions should be directed. It is important that this Guidance reflect a consensus of the various involved Divisions to minimize the potential for conflicting advice in the design of clinical programs. Where appropriate, this Guidance should indicate which other guidances and resources should be consulted, particularly in aspects that are undergoing ongoing examination and evolution of policy, such as surrogate endpoints, biomarkers, and accelerated approval.

For many years the assessment of new therapies for SLE has been based on case reports, anecdotal retrospective series, and small, single-center clinical trials. Patient selection biases, lack of heterogeneity of patient populations, confounding effects of concomitant medications, and the absence of contemporaneous controls have made these reports difficult to interpret when seeking prospective evidence-based data. Many reports include either small numbers of patients in controlled trials that lack statistical power to draw conclusions, or are uncontrolled anecdotal series or individual case reports. Among the larger controlled trials, a serious issue in the failure to reach statistical significance may be the initial study design. There is a need to discuss the deficiencies of trial design and statistical limitations of the above using historical examples to make clear the FDA's position and expectations for future clinical trials. This would seem especially important

for the view on the use of cyclophosphamide in lupus nephritis, which is the most widely prescribed drug for lupus nephritis (Houssiau, Lupus 2005), but has never even been submitted for regulatory review for this indication.

Although most FDA guidance for industry documents follow a similar style and content as the present draft, there are some exceptions to the rule. "Cancer Drug and Biological Products – Clinical Data in Marketing Applications, October 2001" includes a fictitious example to carefully and clearly illustrate the agency position. The FDA "Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA), February 1999" supplies useful examples regarding the application of end-points, interpretation of surrogate end-points in accelerated approval for RA and how the Agency thinks about the issues in general. These types of illustrative examples would prove extremely helpful for sponsors attempting to prepare a clinical development plan for SLE therapy.

Comments on specific sections

Section II (Background)

Lines 65-66 (also Section IV.B [Effectiveness in the Treatment of a Specific Organ Manifestation])

Guidance text: *It is important that any therapy that claims to improve disease in one organ system not worsen disease elsewhere. In addition to the primary outcome measure selected for a given trial in SLE, every trial should also assess other aspects of the disease process, as this information may be informative about the overall risk-benefit assessment (see Section VII, Risk-Benefit Assessment).*

Comment: Aspreva agrees that a full evaluation will include assessment of lupus activity in both the specific organ being studied as well as other organs and signs and symptoms. However, approvability should be based on a risk-benefit assessment. If a product improved survival or more critical organ-specific manifestations and resulted in worsening of symptoms or lesser organ-specific manifestations, the risk-benefit ratio might be acceptable and the product worthy of consideration for approval. The clinical decision should be left to the prescribing physician who can evaluate the level of risk that is acceptable in exchange for potential benefit for a particular patient. The Agency should consider recommending one or more specific measures that can be used as a secondary endpoint in organ-specific studies, and provide information for product labeling to be used in clinical decision making. The British Isles Lupus Assessment Group (BILAG) scale was developed by rheumatologists, has been in use for more than 20 years and has come to be accepted in the medical community as one of the most appropriate measures for overall assessment of outcome and change of disease status over time. BILAG isolates change in status of organ-specific symptoms, and therefore appears to fit this requirement. If the Agency is not prepared to recommend a scale, the Guidance should offer a description of the characteristics of an acceptable scale.

Section III (Measurement of disease activity and clinical outcomes)

General comment: This section does not discuss steroid sparing as an efficacy endpoint, which, given steroid toxicity, is a clinically important therapeutic goal. Specific discussion as to how to best assess steroid sparing as an endpoint or covariate should be included in this document. The issue was extensively discussed at an Arthritis Advisory Committee Meeting reviewing prasterone (GL701; Genelabs Technology Inc., 19 April 2001 http://www.fda.gov/ohrms/dockets/ac/cder01.htm#Arthritis) .

The majority of discussion, here and elsewhere, centers on lupus nephritis. Given that lupus has equally severe manifestations in other systems (eg, cerebral, pulmonary), the Agency should provide its assessment of the status of single organ assessments guidance as to acceptable outcome measures for these systems, or if such outcome measures are not yet developed, the expected quality assessments of these outcome measures. Also it would be helpful to include FDA's experience in the evaluation of other challenging and relatively common disorders in SLE e.g. cognitive dysfunction. Where appropriate, the readers' attention should be directed to other relevant Agency guidances.

Lines 109-119

Guidance text: *There has been considerable interest in the development of a responder index to measure response to therapy on an individual basis. Some proposed definitions of a responder specify a minimum improvement in a measure of disease activity with no worsening in other aspects of lupus.*

Comment: The various measures of SLE (disease activity, damage, patient-assessed response and quality of life) are heterogeneous and poorly correlated, and are generally thought to assess different aspects of disease (Arthritis Advisory Committee meeting minutes, September 29-30, 2003). A responder analysis may therefore lose power when transforming ordinal scale results from these measures to a single categorical outcome of responder/nonresponder. As well, a composite responder index incorporating these various measures may not be clinically meaningful and may not be able to differentiate treatment effects, especially when there is a differential treatment benefit or risk depending on the SLE measure. As an alternative, various efficacy measures may be analyzed as distinct multiple endpoints. An analysis of multiple endpoints with carefully selected adjustment for multiple comparisons may result in gains in power and also present a more accurate picture of the risk/benefits associated with treatment. The advantages and disadvantages of each approach should be discussed. In order to differentiate treatment effects on various manifestations of SLE, the various types of endpoints should be reported separately. Given the variety of measures available, the Agency is urged to accept BILAG as an appropriate primary endpoint for studies of general disease activity, and a suitable secondary endpoint for organ-specific trials. As mentioned previously, BILAG has been in use for over 20 years and can be readily adapted for trial use.

Lines 124-125
***Guidance text**: Studies that measure disease activity at fixed time points may miss flares in between study assessments.*

Comment: The Guidance needs to state how the studies need to be designed to avoid missing flares in terms of the optimal frequency of flare measurements, or recommendations for study design if fixed time-point measurements are inappropriate. The advantages and disadvantages of various flare definitions should be discussed.

Lines 144-146
***Guidance text**: The SLICC/ACR Damage Index measures only changes that have been present for at least six months; therefore, only longer-term clinical trials could demonstrate reduction in the rate of progression of damage using this measure.*

Comment: The guideline does not make clear how long the studies using this index would need to be. Durations are detailed in the September 2003 Advisory Committee meeting transcript, and in the Concept papers. These durations should be stated in the guideline.

Lines 176-192; also Section IV.B Lines 330-351 and Section Section VI Lines 695-697
***Guidance text**: After a diagnosis of lupus nephritis is established, disease activity is assessed clinically by examination of the urinary sediment and by measures of renal function. A variety of outcome measures have been used in clinical trials of lupus nephritis to assess organ-specific disease activity. Mortality is an important outcome measure, but low mortality rates and long observation times make it a relatively insensitive measure in clinical trials. Measures of renal function can be used as outcome measures, including progression to end-stage renal disease (ESRD), sustained doubling of serum creatinine, creatinine clearance, and iothalamate clearance, for full approval. Other measures may also be suitable and can be employed in therapeutic studies if sufficient data to support the proposed measure are available. The use of the doubling of serum creatinine is the best-validated of these measures as it has been shown to reliably predict long-term renal outcomes; however, it is insensitive to smaller changes that represent earlier signs of damage that are nonetheless clinically important. Changes in the urine protein/creatinine ratio may serve as an indicator of the need for further assessment with a 24-hour urine collection for quantitation of the extent of proteinuria and impairment in renal function as measured by creatinine clearance. We recommend investigators design trials to minimize confounding variables (Boumpas 1998) as these can complicate interpretation of renal function measures, including serum creatinine and creatinine clearance.*

Comment: In clinical practice it is standard to intervene prior to doubling of serum creatinine, since, as the draft Guidance points out, it is insensitive to early changes and a positive signal represents disease potentially too advanced for optimal outcome.

Furthermore, the draft Guidance suggests that doubling of serum creatinine be maintained for at least six months to function as an outcome measure. As doubling of serum creatinine generally is considered an indication to use more aggressive therapy and would necessitate withdrawal from a clinical trial that did not include intensification of therapy in its design, it would not be ethical to include this in the definition. In other diseases, surrogates are accepted that are both clinically meaningful and feasible in time-scale, for example, in diabetic nephropathy, HbA1c, and in transplant, 6-month rejection rates. Aspreva suggests that the Agency consider urine protein:creatinine ratio as an appropriate surrogate endpoint. As an alternative to providing criteria for duration, Aspreva suggests providing criteria for confirmation, e.g. that abnormal values should be confirmed by a second measurement, one month later.

Lines 187-189; Lines 404-405

Guidance text: *Changes in the urine protein/creatinine ratio may serve as an indicator of the need for further assessment with a 24-hour urine collection for quantitation of the extent of proteinuria and impairment in renal function as measured by creatinine clearance.*

Comment: Change in the urine protein/creatinine ratio is an accepted endpoint indicating improvement or worsening of proteinuria. (K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease, 2004). Aspreva believes that the Guidance should recognize this assessment as an appropriate measure of proteinuria.

Lines 194-200

Guidance text: *Changes in urinalysis can provide important information for the assessment of renal inflammation in lupus nephritis. The presence of cellular casts and hematuria, when measured accurately, is considered a sensitive indicator of the level of activity of lupus nephritis. However, central laboratories may be unreliable in assessing the presence of casts as they can break up during transport. There is no consensus on the appropriate evaluation of urine sediment. Local or central laboratories could be used if the chosen method is shown to be accurate and reproducible.*

Comment: This paragraph implies that quantitative change in urine sediment findings, in itself, is an appropriate efficacy endpoint. As is noted, accurate assessment of cellular elements and casts in the urine sediment is difficult to achieve at either local or central laboratories. It is more appropriate to use only urine sediment findings as one component of the definition of remission (i.e. normalization) or flare (i.e. worsening).

Lines 211-213

Guidance text: *Increases in proteinuria in patients with other forms of glomerulonephritis may not translate into unfavorable long-term outcomes, and, therefore, measures of proteinuria are not adequate to address clinical outcomes.*

Comment: The draft Guidance suggests that worsened proteinuria is not necessarily associated with worse prognosis. In fact, increases in proteinuria have been correlated with worsening prognosis in other forms of renal disease, as protein excretion in itself is toxic to the kidneys. In a multivariate analysis of 352 patients with proteinuric non-diabetic chronic nephropathies, hypertension and level of proteinuria were independent predictors of change (decrease) in GFR and progression to end stage renal failure (Ruggenenti, 1998). Decrease in proteinuria is a meaningful therapeutic goal to prevent further renal damage, and this outcome should be included in the Guidance. Aspreva believes that a 50% decrease in urine protein:creatine ratio is a valid surrogate endpoint.

Lines 239-241
***Guidance text**: As with any instrument, HRQL instruments used in clinical trials of SLE should undergo validation regarding content validity (inclusion of all relevant domains), construct validity, sensitivity to change, and other criteria.*

Comment: It would be appropriate that the Guidance clarify which HRQL instruments are sufficiently validated to serve as efficacy endpoints in clinical trials designed for registration. As a validated instrument, SF-36 should be included in the Guidance. If a sponsor chooses an instrument other than those included in the Guidance, it will be clear that the responsibility for validation lies with the sponsor.

Section IV (SLE Claims)

General comments: This section is very helpful in that it provides the three main types of claims that companies may be granted. However, this section does not go far enough in demonstrating what is required for registration. Sufficient experience has been gained in this area of clinical research that it should be possible to provide study outlines that companies can use as a guide in developing their programs. This section should also state the specific circumstances under which a single pivotal study may be sufficient for registration.

The accepted treatment strategy of SLE includes induction treatment of patients with active disease and maintenance treatment of patients with stable disease activity. (Cameron, 1999; Balow and Austin, 2004). Different agents are used in these two phases and each has different treatment goals. Aspreva suggests that the claim structure for lupus incorporate these treatment goals and that the claims be identified as "induction treatment" and "maintenance treatment". These claims are clinically meaningful and reflect current treatment practice. For a claim of "induction treatment", measures of improvement such as partial response, complete response and complete remission would be demonstrated in a patient population meeting criteria for active disease. For a claim of "maintenance treatment", measures of stabilization of disease and/or reduction in the time to flare or the number of flares would be appropriate endpoints, demonstrated in a patient population without evidence of active disease. Efficacy in a specific organ likewise should be considered as induction, maintenance, or both. Aspreva also suggests that

treatment duration required for such claims needs to be clarified in the Guidance. The Agency should also clarify if a reduction in disease activity or other endpoints requires to be sustained and if so for how long in order to achieve a claim.

Lines 330-334

Guidance text: *1) Incidence of mortality and progression to end stage renal disease. Mortality and ESRD (when clearly defined prospectively) are objective, reliably determined, and the endpoints of ultimate importance. However, studies using these as the endpoint will generally require longer duration and larger sample size than may be needed when other endpoints are used.*

Comment: This study endpoint is listed as number 1. It is complex and costly for studies evaluating mortality and progression to end stage renal disease to be conducted in advance of the initial registration. In Aspreva's opinion, guidance on surrogate endpoints, with mortality and progression to end stage renal disease being evaluated in Phase 4 studies, after the initial conditional registration, should be added as an option in the draft Guidance.

The statement – *Data showing that the measure of improvement is associated with improved patient outcomes can contribute to supporting the conclusion that the surrogate is reasonably likely to predict clinical benefit,* needs to go further by indicating what is required to predict clinical benefit in the studies conducted prior to registration.

Lines 373-388

Guidance text: 4) *Induction of renal remission. Active lupus nephritis is associated with evidence of renal inflammation, including cellular casts, proteinuria, and decreases in renal function. Organ-threatening WHO class III and IV lupus nephritis is frequently treated with cyclophosphamide and high doses of corticosteroids, agents that are associated with significant toxicity. A treatment that induces a sustained remission in lupus nephritis would confer a clinical benefit. Clinical studies of lupus nephritis use varied definitions of renal remission, but generally specify decreases in hematuria and cellular casts, decreases in proteinuria, and stabilization or improvement in renal function. A clinical trial intended to demonstrate induction of renal remission would specify a definition of renal remission that includes all relevant parameters. We recommend providing evidence supporting an association with improved clinical outcome (e.g., decreased likelihood of developing end-stage renal disease or need for dialysis) to defend the selected definition of renal remission. Because of concerns that patients with an inactive urinary sediment may nonetheless progress to renal failure, we recommend that studies using renal remission as an outcome measure include follow-up renal biopsies in at least a subset of patients.*

Comment: In Aspreva's opinion, decreased likelihood of ESRD is not an appropriate outcome to focus on. It is low-frequency within the usual time-frame of a clinical trial,

requires years'-long follow-up to see a difference between groups (Illei, 2001; Chan, 2005), making trial design even more challenging and a successful application unlikely.

Section V Trial Design and Analysis

General comment: The FDA will not determine whether industry research should focus on the management of patients with rapidly progressive disease or the longer term management of relatively quiescent disease. However, these two therapeutic extremes require very different approaches in drug development. Some of the challenges in trial design include: composite lupus activity scales versus measures of individual organ dysfunction, cumulative response over time versus response at some predetermined future time point, improved safety versus superior efficacy, choice of statistical methodology etc. Some of the choices will be obvious depending upon the population under study. Some choices will be less obvious. For example, if the frequency of flare is an end-point, the choice of observational time points will be critical to the assessment of efficacy. It would be helpful to include more detailed thinking from the authors and to have illustrated the above points with case studies.

Lines 495-498
Guidance text: *Another approach is to use an AUC analysis based on disease activity assessments at intervals throughout the trial. An AUC analysis may more comprehensively measure disease activity during the study than at a single time point. However, AUC differences need to be interpreted carefully.*

Comment: The Agency suggests that an AUC analysis of disease activity may be used. Could the agency clarify if any utility of AUC may be made for a primary endpoint and in what context an AUC analysis would be acceptable to the Agency. For example, the BILAG itself covers disease activity over the previous month, and if this disease activity measure were applied for the duration of the study and an AUC applied to the BILAG would this be considered as a clinically valid interpretation of the efficacy response?

Lines 532-534
Guidance text*: To explore the generalizability of the benefits seen, we recommend subset analyses be carried out regarding the extent of benefit for disease affecting specific organ systems.*

Comment: This recommendation appears to be in conflict with the general position of the FDA regarding subset analyses. Typically, subset analyses are viewed skeptically by the Agency unless strong statistical support is justified. Findings from subset analyses in clinical trials may lead to erroneous conclusions and should be interpreted with extreme caution when addressing the issue of generalizability. Treatment groups within a subset may be imbalanced with respect to risk factors that independently affect outcome. If patients have dysfunction in multiple organs, subset analyses are performed on overlapping samples which further complicates the interpretation. The formulation of

specific hypotheses for selected organ classes and HRQL indices may provide some additional rigor. The Guidance should also mention other considerations that are relevant to the investigation of generalizability.

Lines 592-609

Guidance text: *Studies to demonstrate the improved safety profile of a new drug compared to standard therapy may also be considered. We recommend these trials also be of adequate duration to establish efficacy. If comparable efficacy is expected, rather than superior efficacy, then a noninferiority design to evaluate efficacy will be necessary. Rigorous noninferiority demonstrations are necessary, but can be difficult to achieve. It is recommended that sponsors proposing such studies identify the known effect size for the comparator and define a noninferiority margin that preserves a sufficient percentage of the effect size to demonstrate efficacy with the new product. These choices must be based on careful and comprehensive review of the data available regarding the comparator agent. It is also important for these studies to be powered to demonstrate that the new product is noninferior and to adequately assess the claim of an improved safety profile. It is appropriate for steroid sparing agents to demonstrate not only that reduction in steroid use is statistically significant, but also that these reductions translate into an improved safety profile. Ensuring that a trial has sufficient power to demonstrate improved safety may be problematic in lupus, although studying a collection of important adverse events may help in this regard. Other trial designs may be considered but it is recommended that these be discussed with the appropriate reviewing division before initiation.*

Comment: The issue of non-inferiority requires further discussion and more detailed guidance from the Agency, given that the standards of care for active SLE (from a regulatory perspective) are not defined and that historical evidence of the efficacy of the standard of care agents used (such as cyclophosphamide) compared to placebo is insufficient. As detailed in the draft Guidance, the demonstration of non-inferior efficacy and superior safety to a known agent used in the treatment of SLE are likely objectives of clinical development of new drugs for this indication. To date, there have been no acceptable drugs approved for lupus nephritis that would serve as comparators for a non-inferiority design. Until such time as a drug is approved, it would appear that designing an acceptable non-inferiority trial in lupus nephritis is not possible. If this is not the Agency's position, more specific guidance is required as to how to determine an acceptable margin or estimate parameters for the comparator treatment to determine non-inferiority.

Section V.D Other Trial Design Issues

General comment: Aspreva suggests that the Guidance discusses other trial design issues, such as stratification of the randomization for factors that may affect outcomes, when it might be appropriate to use internal pilot studies, combined Phase II/III designs,

study designs that combine induction treatment and maintenance phase treatments in a single trial, and other adaptive/flexible designs.

Lines 630-635

***Guidance text**: Blinding is intended to minimize the potential biases resulting in differences in management of patients or assessment of patient status. Therefore, it is important that every effort be made to ensure that trials are adequately blinded. This can require, among other things, identification of third parties to assess efficacy, to administer drugs, or to make patient management decisions.*

Comment: Aspreva recommends that while the preference may be for a blinded study design that the FDA also acknowledge the difficulties associated with a blinded design, particularly where those designs use IV cyclophosphamide as comparator. In Aspreva's view it would be unethical to attempt to blind intravenous cyclophosphamide administration by a double-dummy strategy, given the requirement for protective hydration (in renally compromised subjects), intravenous infusion and, as part of best practice, premedication for nausea prophylaxis and gonadal protection. Additionally, comparisons between disparate dosage forms and/or administration regimens can render blinding an insurmountable challenge. It should be suggested that there are alternative ways to minimize bias, such as third party adjudication committees, rigorous, well designed study parameters, objective endpoints, and centralized training/monitoring of study investigations and personnel. ICH-9 offers the following advice, and should be cited.

> "Single-blind and open-label trials provide additional flexibility, but it is particularly important that the investigator's knowledge of the next treatment should not influence the decision to enter the subject; this decision should precede knowledge of the randomized treatment. For these trials, consideration should be given to the use of a centralized randomization method, such as telephone randomization, to administer the assignment of randomized treatment. In addition, clinical assessments should be made by medical staff who are not involved in treating the subjects and who remain blind to treatment. In single-blind or open-label trials every effort should be made to minimize the various known sources of bias and primary variables should be as objective as possible. The reasons for the degree of blinding adopted should be explained in the protocol, together with steps taken to minimize bias by other means. For example, the sponsor should have adequate standard operating procedures to ensure that access to the treatment code is appropriately restricted during the process of cleaning the database prior to its release for analysis." (ICH-9)

Section VI Surrogate Markers as Endpoints

General Comment: A conference was held at the FDA in 2003 on the use of biomarkers and surrogate endpoints in the design of clinical trials for SLE (Schiffenbauer J et al.

Arthritis Rheum. 2004; 50:2415-2422). More recently, candidates for surrogacy include C-reactive protein auto-antibodies and a variety of cytokine receptors. Novel imaging techniques may aid our understanding of cognitive dysfunction. The guidelines do not discuss these more experimental end-points, their potential relevance and statistical methodology specific to SLE. The Guidance should clarify its expectations for the process of validation of a surrogate marker, and what it means for a surrogate to reasonably predict clinical benefit. The Guidance should define the Agency's position on the combined use of clinical end-points with experimental surrogate markers to ensure the timely completion of trials where it is impractical to recruit large numbers of patients with SLE. Although the accelerated drug approval process (Subpart H) is available with the commitment to provide more clinical trial data post registration, the guideline should clarify the Agency's thinking on these issues specifically related to SLE, particularly as it affects those divisions involved in the review of SLE-related applications.

Lines 771-797 References

Comment: The most recent reference included dates from 1998, and the draft Guidance does not include the more recent publications on endpoints and study design in lupus, reflecting the current interest and activity in the field. We suggest considering the following for inclusion:

Ad Hoc Working Group on Steroid-Sparing Criteria in Lupus. Criteria for steroid-sparing ability of interventions in systemic lupus erythematosus: report of a consensus meeting. Arthritis Rheum. 2004 Nov;50(11):3427-31.

American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria. The American College of Rheumatology response criteria for systemic lupus erythematosus clinical trials: measures of overall disease activity. Arthritis Rheum 2004 Nov;50(11):3418-26.

Illei GG, Lipsky PE. Biomarkers in systemic lupus erythematosus. Curr Rheumatol Rep. 2004 Oct;6(5):382-90.

Kozora E, Ellison MC, West S. Reliability and validity of the proposed American College of Rheumatology neuropsychological battery for systemic lupus erythematosus. Arthritis Rheum. 2004 Oct 15;51(5):810-8.

Schiffenbauer J, Hahn B, Weisman MH, Simon LS. Biomarkers, surrogate markers, and design of clinical trials of new therapies for systemic lupus erythematosus. Arthritis Rheum. 2004 Aug;50(8):2415-22.

Strand V. Clinical trial design in systemic lupus erythematosus: lessons learned and future directions. Lupus. 2004;13(5):406-11.

Schiffenbauer J, Simon LS. Randomized controlled trials in systemic lupus erythematosus: what has been done and what do we need to do? Lupus. 2004;13(5):398-405.

References for comments

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Brenner BM, Cooper ME, deZeeuw D, et al: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001:345:861-869.

Chan TM, Tse KC, Tang CS, Lai KN, Li FK. Long-term outcome of patients with diffuse proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide followed by azathioprine. Lupus. 2005;14:265-72.

Cameron JS. Lupus nephritis. J Am Soc Nephrol 1999;10:413-424.

Houssai FA. Cyclophosphamide in lupus nephritis.Lupus. 2005;14:53-8.

Illei GG, Austin HA, Crane M, et al. Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. Ann Intern Med. 2001;135:248-57.

International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use. ICH Harmonised Tripartite Guideline Statistical Principles For Clinical Trials (E9).

K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004:43(5 Suppl 1):S1-290.

Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G. Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN). Kidney Int 1998;53(5):1209-1216.